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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/363,100	07/29/1999	DONALD A.G. MICKLE	50074/004003	7723

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER
AFREMOVA, VERA

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 06/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/363,100	Mickle et al.
Examiner	**Art Unit**
Vera Afremova	1651

-- The MAILING DATE of this communication appears on th cover sheet with the c rresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 2, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 4-11, and 14-24* is/are pending in the application.

4a) Of the above, claim(s) *14-24* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-6, 10, and 11* is/are rejected.

7) ☒ Claim(s) *7-9* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/02/2003 has been entered

Claims 1, 2 and 4-11 as amended [Paper No. 20 filed 12/26/2003] are under examination in the instant office action.

Claims 13 and 25-28 have been canceled by applicants [Paper No. 20 filed 12/26/2003].

Claims 3, 12, 29 and 30 were canceled by applicants. [Paper No. 16 filed 4/16/2002].

Claims 14-24 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions. Election was made without traverse in Paper No. 7 filed 12/11/2000.

Claim Objections

Claim 6 is objected to because of the following informalities:

There is some typing error, for example: symbol "-" between numbers 1 and 2.

Appropriate correction is required.

Response to Arguments

Applicant's arguments filed 12/26/203 [Paper No. 20] have been fully considered but they are not all found persuasive for the reasons below.

Applicant's arguments are found persuasive with regard to the cited references US 5,602,301 [IDS-10-8], Robinson et al. [U], Murry et al. [IDS-10-31], US 5,736,396 [A] and Wakitani et al. [IDS-10-37]. The cited US 5,602,301 [IDS-10-8] and the references by Robinson et al. [U] and Murry et al. [IDS-10-31] teach methods for improving heart function by administering differentiated cells such as skeletal myoblasts and/or cardiomyocytes which are cells different from the presently claimed mesenchymal stem cells (MSC) and these cited references do not suggest administration of MSC (response page 7, par. 1-3).

The cited US 5,736,396 [A] teaches administration of MSC to a patient in need thereof but it does not disclose treating a patient having a cardiac scar tissue and it does not demonstrate improvement in heart function as argued by applicants (response page 8, last par.).

Wakitani et al. [IDS-10-37] suggests the use of the 5-aza-pretreated MSC and/or partially differentiated MSC as a source of cells for transplantation and myogenic regeneration but it does not disclose *in vivo* application of the pretreated MSC and it does not demonstrate survival of the MSC in cardiac scar tissue (response pages 7-8).

Thus, the rejection of claims over US 5,602,301 [IDS-10-8], Robinson et al. [U], Murry et al. [IDS-10-31], US 5,736,396 [A] and Wakitani et al. [IDS-10-37] have been withdrawn.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4-6 and 9-11 as amended are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/03973 [IDS-13-1].

Claims are directed to a method for improving heart function in a patient having cardiac scar tissue wherein the method comprises administering to said cardiac scar tissue a cellular suspension containing mesenchymal stem cells (MSC) wherein said administered cells survive in said scar tissue and improve hear function in said patient. Some claims are further drawn to the use of MSC which are isolated from bone marrow, cultured prior administration and autologous. Some claims are further drawn to the use of MSC which are induced to differentiate prior administration and/or co-cultured with cardiomyocetes. Some claims are further drawn to administration of MSC by injection.

WO 99/03973 [IDS-13-1] discloses a method for regeneration and repair of damaged cardiac muscle including cardiac muscle damaged (page 2, line 30) through disease or degeneration by administering a cell suspension with MSC (page 2, par. 3). The cited patent teaches the use of MSC as a therapy for congestive heart failure (page 2, line 21) and, thus, it encompasses administration of MSC to the same patient having cardiac scar tissue or into the same cardiac scar tissue as encompassed by the presently pending claims and in the light of specification (see specification from page 1, line 19 to page 2, line 4). The cited patent teaches

that the heart environment improves differentiation of MSC into cardiomyocetes (page 10, line 9) and that MSC survive or integrate into surrounding myocardium (page 4, lines 4-6). WO 99/03973 also teaches that MSC are administered by injection (page 3, line 23) and that the administered MSC are obtained from bone marrow (page 3, line 11). The method of the cited patent comprises administration of autologous cells (page 3, line 18). The cited patent also teaches that the administered MSC are cultured prior administration and/or they are genetically modified or engineered during culturing (page 4, par. 2). The administered MSC compositions or MSC suspensions are mixtures of cells or co-cultures of unmodified MSC and modified MSC (page 4, par. 3). The cited patent also suggests the use of a partially differentiated mixture containing MSC in order to shorten the time required for complete cell differentiation after administration (page 4, last paragraph) wherein the partially differentiated mixture comprises undifferentiated MSC and differentiated MSC which are cardiomyocetes. Thus, the cited patent teaches administration of co-culture of MSC and cardiomyocetes.

The cited patent WO 99/03973 [IDS-13-1] is lacking disclosure about the use and effects of MSC which have been induced to differentiate prior administration by exposing cells to 5-azacytidine.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to administer MSC to cardiac scar tissue for the expected benefits in improving heart function as taught by WO 99/03973 [IDS-13-1]. The method of the cited WO 99/03973 is substantially similar, if not identical, to the presently claimed method

because it encompasses administration of similar, if not identical, cell suspensions. The administered MSC of the cited patent are autologous, derived from bone-marrow, cultured, modified or pretreated, induced to differentiate and present in co-culture with cardiomyocetes. The method of the cited WO 99/03973 is substantially similar, if not identical, to the presently claimed method because it encompasses MSC administration to a similar, if not identical, patient having cardiac scar tissue. The cited patent teaches the use of MSC as a therapy for congestive heart failure and, thus, it encompasses administration of MSC to the same patient having cardiac scar tissue or to the same cardiac scar tissue as encompassed by the presently pending claims in the light of specification (specification from page 1, line 19 to page 2, line 4). Thus, the claimed invention is prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited reference. Therefore, the claims are properly rejected under 35 U.S.C. 103.

However, the subject matter of claims 7-9 is considered to be free from the prior art of record in the light of unexpected results disclosed by applicant. On specification page 23, par. 2 applicant discloses that the injection of the 5-aza-pretreated MSC, which have been induced to differentiate prior administration, yields superior results in terms of improving heart function over the injection of fresh or cultured or co-cultured MSC.

Claims 7-9 are objected to as being dependent upon a rejected base claim, but would be allowable if claim 7 is rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following claim is drafted by the examiner and considered to distinguish patentably over the art of record in this application, and is presented to applicant for consideration:

A method for improving heart function in a patient having cardiac scar tissue, said method comprising administering by injecting to said cardiac scar tissue a cellular suspension containing mesenchymal stem cells which have been induced to differentiate into cardiomyogenic cells prior to administration by contacting with 5-azacytidine wherein said administered cells survive in said scar tissue and improve hear function in said patient.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

Art Unit 1651 VERA AFREMOVA

June 13, 2003 PATENT EXAMINER